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December 28, 2001

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Commissioner for Patents
Washington, D.C. 20231

PCT/JP00/04203
-filed June 27, 2000

Re: Application of Kozo AOKI, Kazuhiro AIKAWA, and Masayuki KAWAKAMI
BENZIMIDAZOLE COMPOUNDS AND MEDICAMENTS COMPRISING THE SAME
Assignee: FUJI PHOTO FILM CO., LTD.
Our Ref: Q67718

Dear Sir:

The following documents and fees are submitted herewith in connection with the above application for the purpose of entering the National stage under 35 U.S.C. § 371 and in accordance with Chapter II of the Patent Cooperation Treaty:

☑ an English translation of the International Application.

☑ an International Search Report and Form PTO-1449 listing the ISR references.

☑ an English translation of the International Preliminary Examination Report.

☑ a Notification Concerning Submission or Transmittal of Priority Document.

The Declaration and Power of Attorney, Assignment, will be submitted at a later date.

It is assumed that copies of the any Articles 19 and 34 amendments as required by § 371(c) will be supplied directly by the International Bureau, but if further copies are needed, the undersigned can easily provide them upon request.

The Government filing fee is calculated as follows:

Total claims	22	-	20	=	2	x	$18.00	= $36.00
Independent claims	2	-	3	=		x	$84.00	= $.00
Base Fee								$890.00
Multiple Dependent Claim Fee								$280.00
TOTAL FEE								$1206.00

A check for the statutory filing fee of $1,206.00 is attached. You are also directed and authorized to charge or credit any difference or overpayment to Deposit Account No. 19-4880. The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16, 1.17 and 1.492 which may be required during the entire pendency of the application to Deposit Account No. 19-4880. A duplicate copy of this transmittal letter is attached.

Priority is claimed from:

Country	Application No	Filing Date
Japan	11-181142	June 28, 1999

Respectfully submitted,

for Paul A. Mikio Reg. 33,102

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Registration No. 32,197

MXB/rwl

SPECIFICATION

Benzimidazole Compounds and Medicaments Comprising the Same

Technical Field

The present invention relates to benzimidazole compounds useful as active ingredients of medicaments.

Background Art

In recent years, patients with so-called adult diseases such as arterial sclerosis, hypertension, and diabetes mellitus have been continuously increasing with prolongation of life expectancy. In particular, patients with hyperlipidemia and arterial sclerosis derived therefrom have been remarkably increasing due to excessive intake of high calorie and high cholesterol food, which have become a serious social problem. Medications currently applied for treatment of hyperlipidemia and arterial sclerosis are those symptomatically lower cholesterol in blood, and no medicament that can be expected to have potency in retracting arterial sclerosis lesions has been used clinically. Arterial sclerosis is characterized by lesions of intimal hyperplasia and lipid accumulation in blood vessels, and it has been elucidated from recent biochemical findings that foaming of macrophages plays a main role in the formation of arterial sclerosis lesions. Accordingly, suppression of the foaming of macrophages may possibly prevent arterial sclerosis by inhibiting formation of arterial sclerosis lesions, or achieve radicular treatment of arterial sclerosis by retraction of arterial sclerosis lesions. However, no medicament having such activity has been known.

It has been suggested that an inhibitor of ACAT, an enzyme involved in intestinal absorption and metabolism of cholesterol, such as imidazole derivatives described in Bio. Med. Chem. Lett., Vol. 5(2), 167-172 (1995) reduces blood cholesterol level and thus suppresses the foaming of macrophages in an animal experiment (for example, piperazine derivatives described in International Publication WO98/54153). However, since these compounds are directed to ACAT inhibitory activity, they do not achieve satisfactory inhibition of the foaming of macrophages, and their effects are insufficient.

Therefore, an object of the present invention is to provide a compound having

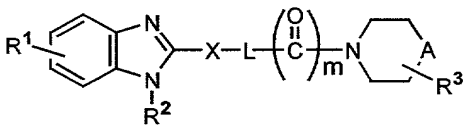
activity of suppressing the foaming of macrophages, and is useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of arterial sclerosis. Another object of the present invention is to provide a compound having the aforementioned activity, and is useful as an active ingredient of medicament for preventive and/or therapeutic treatment of hyperlipidemia.

Disclosure of the Invention

The inventors of the present invention conducted various researches to achieve the foregoing objects, and as a result, they found that novel benzimidazole compounds represented by the formula (I) set out below have activity of suppressing the foaming of macrophages, and are useful as active ingredients of preventive and/or therapeutic medicament of arterial sclerosis and preventive and/or therapeutic medicament of hyperlipidemia.

The compounds represented by the formula (I) according to the present invention have an inhibitory action against the foaming of macrophages independent from the ACAT inhibitory activity, and achieve remarkable effects in preventive and/or therapeutic treatment of arteriosclerosis based on the action. As benzimidazole compounds, available compounds include those known as active ingredients of medicaments for other applications (for example, the compounds of International Patent Publication WO95/34304) or those known as synthetic intermediates for drugs, agricultural chemicals or the like (for example, Chim. Chronika., Vol. 9(3), 239-246 (1980)). However, as demonstrated in the examples, the benzimidazole compounds known so far fail to inhibit the foaming of macrophages, and specific action of the compounds of the present invention are not suggested in view of these compounds.

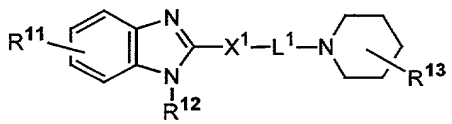
The present invention thus provides benzimidazole compounds represented by the following formula (I):



[in the formula, R^1 represents one or more functional groups on the benzene ring selected from the group consisting of hydrogen atom, a halogen atom, a lower alkyl

group, and a lower alkoxy group; R^2 represents hydrogen atom, an alkyl group, or an acyl group; R^3 represents one or more functional groups (including hydrogen atom) on the ring containing the nitrogen atom and A; A represents O, CH_2 or CH that forms a double bond with an adjacent carbon atom; L represents a C_4-C_8 alkylene group or an ethyleneoxy bridging group represented by $(CH_2CH_2O)_nCH_2CH_2$ (in the formula, n represents 1 or 2); X represents O, S or methylene group; and m represents 0 or 1] and salts thereof.

The present invention also provides benzimidazole compounds represented by the following formula (II):



[in the formula, R^{11} represents one or more functional groups on the benzene ring selected from the group consisting of hydrogen atom, a halogen atom, a lower alkyl group, and a lower alkoxy group; R^{12} represents hydrogen atom, an alkyl group, or an acyl group; R^{13} represents one or more functional groups on the piperidine ring selected from the group consisting of hydrogen atom, an alkyl group, an aryl group, hydroxy group, an alkoxy group, an amino group, an acyl group, cyano group, a carbamoyl group, and an alkoxycarbonyl group; L^1 represents a C_4-C_8 alkylene group; and X represents O, S, or methylene group] and salts thereof.

As other aspects of the present invention, provided are methods for preparing the compounds represented by the aforementioned formula (I) or (II), and medicaments comprising a compound represented by the aforementioned formula (I) or (II) or a physiologically acceptable salt thereof as an active ingredient. As preferred embodiments of the aforementioned medicaments, pharmaceutical compositions are provided which comprise the aforementioned compounds or a physiologically acceptable salt thereof as an active ingredient and an additive for pharmaceutical preparation. The medicaments of the present invention are useful as, for example, those for preventive and/or therapeutic treatment of hyperlipidemia and for preventive and/or therapeutic treatment of arteriosclerosis. The medicaments are also useful as agents for suppressing foaming of macrophages, agents for retracting arterial sclerosis

lesions, and agents for inhibiting formation of arteriosclerotic lesion.

As further aspects of the present invention, provided are uses of the compounds represented by the aforementioned formula (I) or (II) or salts thereof for manufacture of the aforementioned medicaments, and methods for preventive and/or therapeutic treatment of hyperlipidemia and methods for preventive and/or therapeutic treatment of arteriosclerosis, which comprise the step of administering a preventively and/or therapeutically effective amount of the compound represented by the aforementioned formula (I) or (II) or a physiologically acceptable salt thereof to a mammal including human.

Best Mode for Carrying out the Invention

In the specification, a lower alkyl group or a lower alkyl moiety of a functional group that contains the lower alkyl moiety (e.g., lower alkoxy group) may be a linear, branched or cyclic alkyl group, or a combination thereof. For example, an alkyl group having 1-4 carbon atoms (for example, methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, sec-butyl group, tert-butyl group and the like) may be used. A halogen atom referred to in the specification may be any of fluorine atom, chlorine atom, bromine atom and iodine atom.

An alkyl group or an alkyl moiety of a functional group that contains the alkyl moiety (e.g., an alkoxy group, an alkanoyl group and the like) referred to in the specification may be linear, branched or cyclic alkyl group, or a combination thereof. An example includes an alkyl group having 1-8 carbon atoms (e.g., methyl group, ethyl group, butyl group, octyl group and the like), and a preferred example includes an alkyl group having 1-4 carbon atoms (e.g., methyl group, ethyl group, n-propyl group, n-butyl group). An aryl group or an aryl moiety of a functional group that contains the aryl moiety (arylcarbonyl group and the like) is preferably a monocyclic or bicyclic aryl group having a 6- to 10-membered ring, and more specifically, phenyl group, naphthyl group and the like can be used. An alkyl group or an alkyl moiety of a functional group having the alkyl moiety, a lower alkyl group or a lower alkyl moiety of the functional group having the lower alkyl moiety, or an aryl group may have one or two functional groups at any positions. When two or more functional groups exist, they may be the same or different.

Examples of the acyl group include an alkanoyl group, an arylcarbonyl group,

an alkylsulfonyl group, an arylsulfonyl group, an alkoxycarbonyl group, a sulfamoyl group, a carbamoyl group and the like. Examples of the alkanoyl group include an alkanoyl group having 1-8 carbon atoms (e.g., acetyl group, butanoyl group, octanoyl group and the like), preferably an alkanoyl group having 1-4 carbon atoms (e.g., acetyl group, butanoyl group and the like). Examples of the arylcarbonyl group include an arylcarbonyl group having 6-10 carbon atoms (e.g., benzoyl group, naphthoyl group and the like). Examples of the alkoxycarbonyl group include an alkoxycarbonyl group having 1-8 carbon atoms (e.g., methoxycarbonyl group, ethoxycarbonyl group, octyloxycarbonyl group and the like), preferably an alkoxycarbonyl group having 1-4 carbon atoms (e.g., methoxycarbonyl group, ethoxycarbonyl group and the like).

Examples of the alkylsulfonyl group include an alkylsulfonyl group having 1-8 carbon atoms (e.g., methanesulfonyl group, butanesulfonyl group, octanesulfonyl group and the like) and examples of the arylsulfonyl group include an arylsulfonyl group having 6-10 carbon atoms (e.g., benzenesulfonyl group, naphthalenesulfonyl group and the like). Examples of the sulfamoyl group include a sulfamoyl group having 0-8 carbon atoms (e.g., sulfamoyl group, methylsulfamoyl group, diethylsulfamoyl group, octylsulfamoyl group, hexadecylsulfamoyl group, phenylsulfamoyl group and the like), preferably a sulfamoyl group having 0-4 carbon atoms (e.g., sulfamoyl group, methylsulfamoyl group, diethylsulfamoyl group and the like). Examples of the carbamoyl group include a carbamoyl group having 0-8 carbon atoms (e.g., carbamoyl group, methylcarbamoyl group, diethylcarbamoyl group, octylcarbamoyl group, hexadecylcarbamoyl group, phenylcarbamoyl group and the like), preferably a carbamoyl group having 0-4 carbon atoms (e.g., methylcarbamoyl group, diethylcarbamoyl group and the like). The aforementioned acyl group may have on or more functional groups at any position. When two or more functional groups exist, they may be the same or different.

R^1 represents one or more functional groups on the benzene ring selected from the group consisting of hydrogen atom, a halogen atom, a lower alkyl group, and a lower alkoxy group. When R^1 represents two or more functional groups, they may be the same or different, and substitution positions on the benzene ring are not also particularly limited. The halogen atom represented by R^1 may preferably be fluorine atom, chlorine atom, or bromine atom. R^1 may preferably be hydrogen atom, methyl group, methoxy group, or chlorine atom, and more preferably hydrogen atom.

R^2 is preferably hydrogen atom, a C_1-C_4 alkyl group, or a C_1-C_4 alkanoyl group, and most preferably hydrogen atom. L represents a linking group, and more specifically a C_4-C_8 alkylene group (e.g., butylene group, pentamethylene group, hexamethylene group, octamethylene group and the like) or an ethyleneoxy linking group represented by $(CH_2CH_2O)_nCH_2CH_2$ (in the formula, n represents 1 or 2). These linking groups may be linear or branched. The linking group represented by L is preferably an alkylene group having 5-8 carbon atoms (pentamethylene group, hexamethylene group, heptamethylene group, octamethylene group and the like) or the aforementioned ethyleneoxy bridging group, and most preferably an alkylene group having 5 or 6 carbon atoms. X is preferably O or S, and most preferred X is S. Symbol "m" represents 0 or 1, and preferably 0.

A represents O or CH_2, or CH that forms a double bond with an adjacent carbon atom. R^3 represents one or more functional groups, including hydrogen atom, on the ring containing A and the nitrogen atom as ring constituting atoms. The type, substitution position, and number of the functional groups attached to the ring are not particularly limited. Plural functional groups represented by R^3 may bind to each other to form a saturated, partially saturated, or aromatic hydrocarbon ring, or a saturated, partially saturated, or aromatic heterocyclic ring containing one or more hetero atoms (e.g., nitrogen atom, oxygen atom, sulfur atom or the like) as ring constituting atoms. Specific examples of the ring containing A and the nitrogen atom include piperidine ring, morpholine ring, 1,2,3,6-tetrahydropyridine ring, 1,2,3,4-tetrahydroquinoline ring, 1,2,3,4-tetrahydroisoquinoline ring, decahydroquinoline ring, decahydroisoquinoline ring and the like.

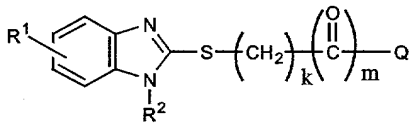
Preferred examples of the functional groups represented by R^3 include hydrogen atom, an alkyl group, an aryl group, hydroxy group, an alkoxy group, an amino group, an acyl group, a cyano group, a carbamoyl group, and an alkoxy carbonyl group, and these functional groups may have one or more further functional groups. The ring containing A and the nitrogen atom is preferably a ring that is not condensed with another ring (specifically, piperidine ring, morpholine ring and the like), and piperidine ring is most preferred. These rings preferably have one or more groups selected from the group consisting of an alkyl group, a hydroxyalkyl group, an aryl group, hydroxy group, and a cyano group as R^3.

Particularly preferred imidazole compounds are represented by the

aforementioned formula (II). Preferred examples of R^{11} and R^{12} are the same as those explained as for the aforementioned R^1 and R^2, respectively. Also as the groups defined by R^{13}, those mentioned above can be suitably used. The alkylene group represented by L^1 may be linear or branched, and examples thereof include butylene group, pentamethylene group, hexamethylene group, octamethylene group and the like. Preferred examples include an alkylene group having 5-8 carbon atoms (e.g., pentamethylene group, hexamethylene group, heptamethylene group, octamethylene group and the like), and particularly preferred example includes an alkylene group having 5 or 6 carbon atoms. X^1 is preferably O or S, and particularly preferred X^1 is S.

R^{11} is preferably hydrogen atom, methyl group, methoxy group, or chlorine atom, and most preferably hydrogen atom. R^{12} is preferably hydrogen atom, a C_1-C_4 alkyl group, or a C_1-C_4 alkanoyl group, and most preferably hydrogen atom. R^{13} is preferably an alkyl group, a hydroxyalkyl group, an aryl group, hydroxy group or a cyano group.

Preferred compounds according to the present invention will be exemplified below. However, the scope of the present invention is not limited to these examples.



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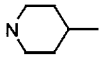
3	5	H	H	0	
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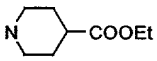
5	5	H	H	0	
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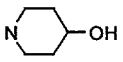
8	5	H	H	0	
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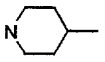
10	6	H	H	0	
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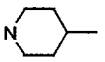
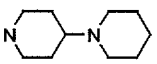
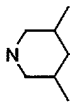
12	4	H	H	1	
13	5	H	H	0	
14	5	H	H	0	

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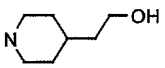
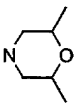
15	5	H	H	0	
16	5	H	H	0	
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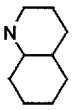
18	5	H	H	0	
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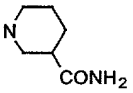
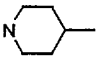
22	5	H	H	0	
23	4	H	H	0	
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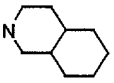
25	5	H	H	0	
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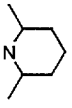
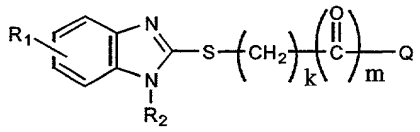
27	5	H	H	0	



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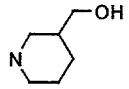
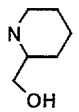
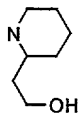
28	5	H	H	0	
29	5	H	H	0	
30	5	H	H	0	
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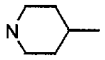
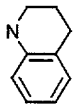
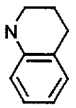
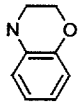
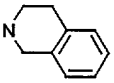
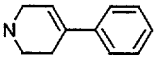
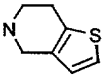
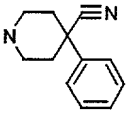
32	8	H	H	0	
33	4	H	H	1	
34	5	H	H	0	
35	5	H	H	0	
36	5	H	H	0	
37	5	H	H	0	
38	5	H	H	0	
39	5	H	H	0	

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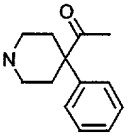
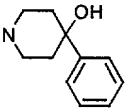
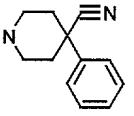
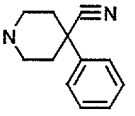
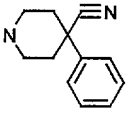
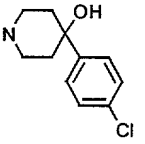
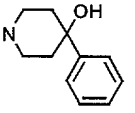
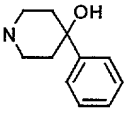
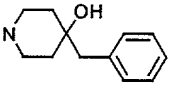
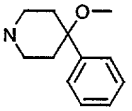
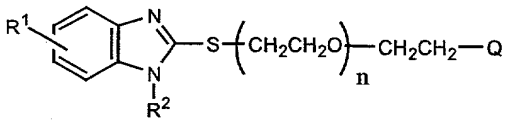
40	5	H	H	0	
41	5	H	H	0	
42	4	H	H	0	
43	6	H	H	0	
44	8	H	H	0	
45	5	H	H	0	
46	6	H	H	0	
47	4	H	H	0	
48	5	H	H	0	
49	5	H	H	0	



No.	R^1	R^2	n	Q
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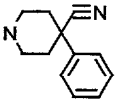
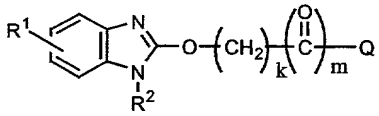
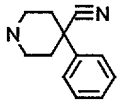
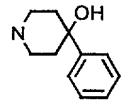
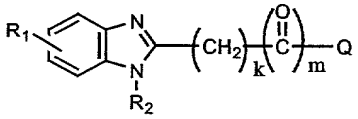
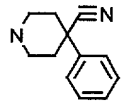
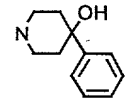
51	H	H	2	
52	H	H	1	
53	H	H	2	
54	H	H	1	



No.	k	R^1	R^2	m	Q
55	5	H	H	0	
56	5	H	H	0	



No.	k	R^1	R^2	m	Q
57	6	H	H	0	
58	6	H	H	0	

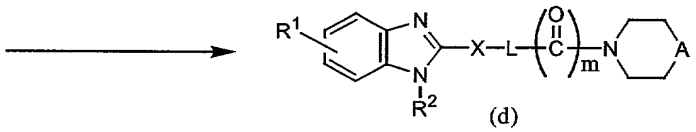
The compounds of the present invention represented by the aforementioned formulas (I) and (II) may form acid addition salts, and such acid addition salts fall within the scope of the present invention. Examples of the acid addition salts include, for example, mineral acid salts such as hydrochlorides, hydrobromides, nitrates, sulfates, and phosphates, and organic acid salts such as p-toluenesulfonates, methanesulfonates, oxalates, tartrates, malates, and citrates. Further, depending on the type of a functional group, they may also form base addition salts. Furthermore, the compounds of the present invention and salts thereof may exist as hydrates or solvates. Any of the compounds in free forms or in the forms of salts, and hydrates and solvates thereof falls within the scope of the present invention.

The compounds of the present invention may have one or more asymmetric carbons depending on the kind of a functional group. In such compounds, stereoisomers such as optical isomers based on one or more asymmetric carbons and

diastereoisomers based on two or more asymmetric carbons may exist. Any of stereoisomers in pure forms, any mixtures of the stereoisomers, racemates and the like fall within the scope of the present invention.

The compounds of the present invention can be prepared from readily available raw material compounds by methods well known to those skilled in the art, for example, in accordance with the following scheme. Specific procedures of these methods are explained in detail in the examples of the specification, and those skilled in the art can easily produce the compounds of the present invention by referring to the general explanations given below and the examples, and by adding suitable alterations or modifications to these methods as required (the symbols used in the scheme have the same meanings as those defined above).

(Formula－1)



(Formula－2)

When X is S, a 2-mercaptobenzimidazole derivative (a) is reacted with a compound (b) having a linking chain (L) (a bi-functional halogeno compound such as a chloride, bromide or iodide, or a sulfonate compound such as tosylate or methanesulfonate and the like, more specifically, dibromopentane, bis-2-chloroethyl ether and the like) to obtain a compound (c) in which one of the functional groups is replaced with the 2-mercaptobenzimidazole derivative. As a solvent, alcohols, acetonitrile and the like can be used, and reaction temperature may be from room temperature to 150°C, preferably about 50°C to 120°C. Further, when a base such as triethylamine is used as an acid scavenger, the reaction may sometimes progress faster, thereby the reaction temperature may be lowered and the reaction time may be shortened.

The compound (b) wherein only one of the functional groups is a halide or sulfonate is subjected to the reaction (the remaining functional group may optionally be hydroxyl group, acetate moiety or the like, and the reaction condition for said

compound may be the same as that mentioned above), and then the resulting compound (c) is subjected to substitution of X' with a halide or sulfonate. For example, substitution from hydroxyl group to a halide or sulfonate can be conducted by a conventional method utilizing tosyl chloride, carbon tetrabromide/triphenylphosphine or the like. The compound (c) as being a halide or sulfonate can be used as a key compound for a reaction with various piperidine derivatives, morpholine derivatives and the like to obtain a target compound (d). As a solvent, alcohols, acetonitrile and the like can be used, and reaction temperature may be from room temperature to 150°C, preferably about 50°C to 120°C. Further, when a base such as triethylamine is used as an acid scavenger, the reaction may sometimes progress faster, thereby the reaction temperature may be lowered and the reaction time may be shortened.

As an alternative method, a piperidine derivative, morpholine derivative or the like can be reacted with a compound (b) as being a halide or sulfonate with a linking chain, and then the product is reacted with 2-mercaptobenzimidazole to synthesize a target compound (d). Depending of reactivity of a compound to be used, it is possible to chose which of the routes is used for the synthesis.

As for compounds wherein m is 1 (having an amide bond), 2-mercaptobenzimidazole (a) and an ω-halocarboxylic acid or ω-halocarboxylic acid ester having a linking chain can be reacted in the same manner as described above to obtain a compound (c) wherein X' is a carboxylic acid (or ester thereof; where the reaction is performed in an alcohol, an ester compound may sometimes be produced when a carboxylic acid is used as a raw material). This compound can be condensed with a piperidine derivative, morpholine derivative or the like to obtain a compound (d). Although it is also possible to directly condense an ester compound and a piperidine derivative, morpholine derivative or the like for the synthesis, it is preferable to convert the carboxylic acid into an acid halide for the reaction, or use an agent for dehydration condensation such as carbodiimide. A compound (d) wherein m is 1 can be reduced with a borane or the like to produce a compound wherein m is 0.

When X is O, a target compound (d) can be obtained by reacting 2-chlorobenzimidazole, of which nitrogen atom at the 1-position of the benzimidazole is protected, with one of hydroxyl groups of a diol compound, then after converting the other remaining hydroxyl group into a sulfonate, reacting the product with a piperidine derivative, morpholine derivative or the like, and finally removing the

protective group. When X is methylene group, the benzimidazole nucleus can be synthesized by heating o-phenylenediamine and ω-hydroxycarboxylic acid in hydrochloric acid, for example, to proceed dehydration condensation. Then, after converting the remaining hydroxyl group into a sulfonate or halide by a conventional method using tosyl chloride or carbon tetrabromide/triphenylphosphine, the product can be reacted with a piperidine derivative, morpholine derivative or the like to obtain a target compound (d).

The compounds of the present invention have a potent activity of suppressing the foaming of macrophages which is involved in the formation of arterial sclerosis lesions in arterial sclerosis. Therefore, the compounds are useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of arterial sclerosis, and an active ingredient of a medicament for preventive and/or therapeutic treatment of hyperlipidemia by lowering blood cholesterol. Although it is not intended to be bound by any specific theory, it has been known that invasion of foamed macrophages into arterial walls triggers hyperplasia of smooth muscles of arterial walls, thereby causing arterial sclerosis (Schaffner, T. et al., Amer. J. Pathol., 110, pp.57-73, 1980; Gerrity, R.G., Amer. J. Pathol. 103, pp.181-190, 1981). The medicaments of the present invention directly inhibit the formation of arterial sclerosis lesions and enables retraction of arterial sclerosis lesions by suppressing the foaming of macrophages which is involved in the formation of arterial sclerosis lesions. Accordingly, the medicaments of the present invention are useful for prevention and/or treatment of arterial sclerosis and hyperlipidemia brought by various causes.

As the active ingredients of the medicaments of the present invention, a substance selected from the group consisting of the compounds represented by the aforementioned formula (I) and salts thereof, and hydrates thereof and solvates thereof can be used. Among the compounds represented by the formula (I), the compounds represented by the formula (II) are preferred. Routes of administration of the aforementioned medicament are not particularly limited, and they can be administered orally or parenterally. Oral administration is preferred. Although the aforementioned substance as the active ingredient, per se, may be used as the medicament of the present invention, it is generally desirable to provide the medicament as a pharmaceutical composition in a form well known to those skilled in the art by adding pharmaceutical additives as required.

Examples of the pharmaceutical composition suitable for oral administration include, for example, tablets, capsules, powders, subtilized granules, granules, solutions, syrups and the like. Examples of the pharmaceutical composition suitable for parenteral administration include, for example, injections, fusion drips, suppositories, inhalants, transdermal preparations, transmucosal preparations, patches and the like. As the pharmaceutical additives, excipients, disintegrating agents or dissolving aids, isotonic agents, pH modifiers, stabilizers, propellants, tackifiers and the like can be used, and they can optionally be used in combination.

For example, for the manufacture of the pharmaceutical composition suitable for oral administration, transdermal administration, or transmucosal administration, usable pharmaceutical additives include excipients such as glucose, lactose, D-mannitol, starch and crystalline cellulose; excipients or disintegrating aids such as carboxymethyl cellulose, starch and carboxymethyl cellulose calcium; binders such as hydroxypropyl cellulose, hydroxypropylmethyl cellulose, polyvinylpyrrolidone and gelatin; lubricants such as magnesium stearate and talc; coating agents such as hydroxypropylmethyl cellulose, sucrose, polyethylene glycol and titanium oxide; bases such as vaseline, liquid paraffin, polyethylene glycol, gelatin, kaoline, glycerol, purified water and hard fat and the like. Further, the pharmaceutical composition can also be produced by using pharmaceutical additives such as, for example, propellants such as frons, diethyl ether and compressed gases; tackifiers such as sodium polyacrylate, polyvinyl alcohol, methyl cellulose, polyisobutylene and polybutene; base fabrics such as cotton cloth, and plastic sheets and the like.

For preparation of the pharmaceutical composition suitable for injection or drip infusion, usable pharmaceutical additives include, for example, dissolving agents and dissolving aids that can form aqueous injections or injections that are dissolved upon use such as distilled water for injection, physiological saline and propylene glycol; isotonic agents such as glucose, sodium chloride, D-mannitol and glycerol; pH modifiers such as inorganic salts, organic acids, inorganic bases and organic bases and the like.

Doses of the medicament of the present invention are not particularly limited, and suitably chosen depending on dosage forms, purpose of administration, i.e., preventive and/or therapeutic purpose, the age, body weight, and symptoms of a patient and the like. For example, for intravenous administration, about 10 mg to

400 mg per day for an adult as the amount of an active ingredient can be administered, and for oral administration, about 10 mg to 800 mg per day for an adult as the amount of an active ingredient can be administered. Preferred doses for an adult are 10 mg to 100 mg per day and 10 mg to 300 mg per day, respectively, as the amount of an active ingredient. The medicament of the present invention may be administered once or several times a day, and any administration period may be applied depending on the age of a patient and improvement of symptoms and the like.

Example

The present invention will be explained more specifically with reference to the following examples. However, the scope of the present invention is not limited to the following examples.

Example 1: Synthesis of 5-(benzimidazoyl-2-thio)pentyl bromide

6.0 g of 2-mercaptobenzimidazole and 60 g of 1,5-dibromopentane were dissolved in 50 ml of ethanol and the mixture was refluxed under heating for 6 hours. After the solvent was evaporated under reduced pressure, the residue was digested with 50 ml of ethyl acetate and 50 ml of hexane to obtain about 12 g of solid. The solid was added with 100 ml of water and neutralized with aqueous sodium hydroxide. The deposited oil-soluble substance was extracted with ethyl acetate, washed with water and concentrated. The residue was purified by silica gel column chromatography (chloroform) to obtain 8.7 g of crude crystals. The crystals were recrystallized from ethanol to obtain 7.8 g of the target title compound (yield: 66%).

Melting point: 126-127°C

MS (FAB^+): m/z 300 (MH^+)

Example 2: Synthesis of 1-(5-(benzimidazoyl-2-thio)pentyl)piperidine (Compound 1)

0.3 g of 5-(benzimidazoyl-2-thio)pentyl bromide and 0.2 g of piperidine were added with 3 ml of acetonitrile and the mixture was refluxed under heating for 5 hours. A small amount of water was added to the reaction mixture to deposit crystals. The crystals were collected by filtration and dried to obtain 0.28 g of the target title substance (yield: 92%).

^{1}H-NMR ($CDCl_3$): (ppm)

1.44 (m, 4H), 1.56 (m, 6H), 1.73 (m, 2H), 2.30 (m, 2H), 2.42 (m, 4H), 3.28 (t, 2H), 7.17 (m, 2H), 7.47 (br, 2H), 10.4 (br, 1H)
MS (FAB$^+$): m/z 304 (MH$^+$)

The following compounds were synthesized in the same manner as in Example 2 by changing the starting material. When crystals were not deposited in the reaction system, water was added and extracted with ethyl acetate, then the organic layer was washed with water and dried over sodium sulfate, and the solvent was evaporated under reduced pressure. Procedure thereafter is specified in the explanation for each compound.

(Compound 2) Purified by silica gel column chromatography (methanol:methylene chloride = 1:10) and then crystallized from ethyl acetate/hexane, yield: 93%.
^{1}H-NMR ($CDCl_3$): (ppm)
1.48 (m, 4H), 1.78 (m, 2H), 2.32 (t, 2H), 2.43 (m, 4H), 3.32 (t, 2H), 3.71 (m, 4H), 7.19 (m, 2H), 7.34 (br, 1H), 7.66 (br, 1H), 9.95 (br, 1H)
MS (FAB$^+$): m/z 306 (MH$^+$)

(Compound 3) Crystallized from water-containing acetonitrile, yield: 95%.
^{1}H-NMR ($CDCl_3$): (ppm)
0.90 (d, 3H), 1.27 (t, 2H), 1.41 (m, 3H), 1.53 (m, 2H), 1.63 (m, 2H), 1.74 (t, 2H), 1.93 (t, 2H), 2.32 (t, 2H), 2.95 (d, 2H), 3.28 (t, 2H), 7.17 (m, 2H), 7.48 (br, 2H)
MS (FAB$^+$): m/z 318 (MH$^+$)

(Compound 5) Purified by silica gel column chromatography (methanol:methylene chloride = 1:10) and then crystallized from water-containing acetonitrile, yield: 75%.
^{1}H-NMR ($CDCl_3$): (ppm)
1.24 (t, 3H), 1.49 (m, 4H) and 1.76-2.02 (m, 8H), 2.31 (m, 3H), 2.88 (brd, 2H), 3.30 (t, 2H), 4.12 (q, 2H), 7.18 (m, 2H), 7.50 (br, 2H), 10.05 (br, 1H)
MS (FAB$^+$): m/z 376 (MH$^+$)

(Compound 8) Purified by silica gel column chromatography (methanol:methylene chloride = 1:5) and then crystallized from water-containing acetonitrile, yield: 88%

^{1}H-NMR ($CDCl_3$): (ppm)

1.4-1.7 (m, 6H), 1.76 (m, 2H), 1.90 (m, 2H), 2.15 (m, 2H), 2.33 (t, 2H), 2.79 (m, 2H), 3.30 (t, 2H), 3.71 (m, 1H), 7.18 (m, 2H), 7.49 (br, 2H)

MS (FAB^+): m/z 320 (MH^+)

(Compound 10) Purified by silica gel column chromatography (methanol:methylene chloride = 1:10) and then crystallized from water-containing acetonitrile, yield: 88%.

^{1}H-NMR ($CDCl_3$): (ppm)

0.90 (d, 3H), 1.29 (m, 4H), 1.45 (m, 4H), 1.64 (d, 2H), 1.72 (m, 2H), 1.75 (m, 3H), 2.30 (m, 2H), 2.95 (d, 2H), 3.29 (t, 2H), 7.18 (m, 2H), 7.49 (br, 2H), 9.9 (br, 1H)

MS (FAB^+): m/z 332 (MH^+)

(Compound 11) Purified by silica gel column chromatography (methanol:methylene chloride = 1:10) and then crystallized from water-containing acetonitrile, yield: 75%.

^{1}H-NMR ($CDCl_3$): (ppm)

1.35 (m, 2H), 1.46 (m, 4H), 1.77 (m, 2H), 2.33 (m, 2H), 2.45 (m, 4H), 3.32 (t, 2H), 3.73 (m, 4H), 7.19 (m, 2H), 7.50 (br, 2H), 9.45 (br, 1H)

MS (FAB^+): m/z 320 (MH^+)

(Compound 13) Purified by silica gel column chromatography (methanol:methylene chloride = 1:5), oil, yield: 93%.

^{1}H-NMR ($CDCl_3$): (ppm)

1.49 (m, 6H), 1.69 (m, 8H), 1.92 (m, 4H), 2.32 (m, 2H), 2.48 (m, 1H), 2.66 (m, 4H), 3.00 (d, 2H), 3.31 (t, 2H), 7.17 (m, 2H), 7.50 (br, 2H)

MS (FAB^+): m/z 386 (MH^+)

(Compound 14) Purified by silica gel column chromatography (methanol:methylene chloride = 1:10), oil, yield: 91%.

^{1}H-NMR ($CDCl_3$): (ppm)

0.85 (d, 6H), 1.46 (m, 7H), 1.71 (m, 5H), 2.33 (dd, 2H), 2.93 (d, 2H), 3.28 (t, 2H), 7.17 (m, 2H), 7.47 (br, 2H), 10.7 (br, 1H)

MS (FAB^+): m/z 332 (MH^+)

(Compound 15) Crystallized from water-containing acetonitrile, yield: 77%.

^{1}H-NMR ($CDCl_3$): (ppm)

1.32 (m, 2H), 1.49 (m, 6H), 1.68 (m, 5H), 1.93 (m, 3H), 2.29 (dd, 2H), 2.96 (d, 2H), 3.29 (t, 2H), 3.68 (t, 2H), 7.17 (m, 2H), 7.48 (br, 2H)

MS (FAB^+): m/z 347 (MH^+)

(Compound 16) Crystallized from water-containing acetonitrile, yield: 75%.

^{1}H-NMR ($CDCl_3$): (ppm)

1.15 (d, 6H), 1.49 (m, 4H), 1.76 (m, 4H), 2.31 (dd, 2H), 2.75 (d, 2H), 3.33 (t, 2H), 3.69 (m, 2H), 7.20 (m, 2H), 7.55 (br, 2H), 9.6 (br, 1H)

MS (FAB^+): m/z 334 (MH^+)

(Compound 17) Crystallized from ethyl acetate/hexane, yield: 58%.

^{1}H-NMR ($CDCl_3$): (ppm)

1.28 (m, 6H), 1.45 (m, 4H), 1.75 (m, 2H), 2.36 (dd, 2H), 2.50 (m, 4H), 3.33 (t, 2H), 3.76 (m, 4H), 7.19 (m, 2H), 7.55 (m, 2H), 9.8 (br, 1H)

MS (FAB^+): m/z 348 (MH^+)

(Compound 18) Purified by silica gel column chromatography (methanol:methylene chloride = 1:10), oil, yield: 85%.

^{1}H-NMR ($CDCl_3$): (ppm)

1.09 (m, 2H), 1.27 (m, 5H), 1.40 (m, 4H), 1.63 (m, 4H), 1.79 (m, 4H), 2.05 (m, 1H), 2.24 (m, 1H), 2.62 (m, 1H), 2.74 (m, 1H), 2.98 (m, 1H), 2.34 (t, 2H), 7.18 (m, 2H), 7.52 (m, 2H)

MS (FAB^+): m/z 358 (MH^+)

(Compound 21) Crystallized from water-containing acetonitrile, yield: 98%.

^{1}H-NMR ($CDCl_3$): (ppm)

0.85 (d, 3H), 1.39 (m, 2H), 1.54 (m, 4H), 1.67 (m, 6H), 1.86 (m, 1H), 2.33 (dd, 2H), 2.94 (t, 2H), 3.27 (t, 2H), 7.16 (m, 2H), 7.47 (br, 2H)

MS (FAB^+): m/z 318 (MH^+)

(Compound 22) Purified by silica gel column chromatography (methanol:methylene

chloride = 1:10), oil, yield: 81%.

^{1}H-NMR ($CDCl_3$): (ppm) 1.50 (m, 4H), 1.59 (m, 2H), 1.73 (m, 3H), 1.92 (m, 1H), 2.09 (m, 1H), 2.32 (m, 2H), 2.57 (m, 1H), 2.74 (m, 1H), 2.88 (m, 1H), 3.37 (t, 2H), 6.91 (br, 2H), 7.17 (m, 2H), 7.49 (br, 2H), 8.2 (br, 1H)

MS (FAB^+): m/z 347 (MH^+)

(Compound 23) Crystallized from water-containing acetonitrile, yield: 69%.

^{1}H-NMR ($CDCl_3$): (ppm)

0.92 (d, 3H), 1.31 (m, 3H), 1.6-1.8 (m, 6H), 1.98 (t, 2H), 2.42 (t, 2H), 2.96 (d, 2H), 3.26 (t, 2H), 7.18 (m, 2H), 7.50 (br, 2H)

MS (FAB^+): m/z 304 (MH^+)

(Compound 24) Crystallized from water-containing acetonitrile, yield: 91%.

^{1}H-NMR ($CDCl_3$): (ppm)

1.08 (d, 3H), 1.3-1.6 (m, 6H), 1.64 (m, 4H), 1.75 (m, 2H), 2.18 (m, 1H), 2.34 (m, 2H), 2.64 (m, 1H), 2.85 (m, 1H), 3.31 (t, 2H), 7.18 (m, 2H), 7.50 (br, 2H)

MS (FAB^+): m/z 318 (MH^+)

(Compound 25) Crystallized from water-containing acetonitrile, yield: 87%.

^{1}H-NMR ($CDCl_3$): (ppm)

1.2-1.9 (m, 19H), 2.2-2.7 (m, 5H), 3.28 (t, 2H), 7.17 (m, 2H), 7.48 (br, 2H)

MS (FAB^+): m/z 358 (MH^+)

(Compound 26) Purified by silica gel column chromatography (methanol:methylene chloride = 1:10), oil, yield: 72%.

^{1}H-NMR ($CDCl_3$): (ppm)

1.68 (m, 2H), 1.81 (m, 2H), 2.41 (t, 2H), 2.47 (m, 4H), 3.33 (t, 2H), 3.73 (m, 4H), 7.20 (m, 2H), 7.50 (br, 2H)

MS (FAB^+): m/z 292 (MH^+)

(Compound 27) Crystallized from water-containing acetonitrile, yield: 91%.

^{1}H-NMR ($CDCl_3$): (ppm)

1.15 (d, 6H), 1.47 (m, 4H), 1.75 (m, 6H), 2.32 (t, 2H), 2.76 (d, 2H), 3.32 (t, 2H), 3.70 (m,

2H), 7.19 (m, 2H), 7.50 (br, 2H), 9.8 (br, 1H)
MS (FAB+): m/z 332 (MH^+)

(Compound 28) Purified by silica gel column chromatography (methanol:methylene chloride = 1:5), oil, yield: 84%.
^{1}H-NMR ($CDCl_3$): (ppm)
1.25 (m, 2H), 1.53 (m, 4H), 1.69 (m, 4H), 1.88 (m, 2H), 2.31 (m, 4H), 2.55 (m, 1H), 2.80 (m, 1H), 3.25 (t, 2H), 3.66 (m, 1H), 3.80 (m, 1H), 7.18 (m, 2H), 7.51 (br, 1H)
MS (FAB+): m/z 334 (MH^+)

(Compound 29) Crystallized from water-containing acetonitrile, yield: 96%.
^{1}H-NMR ($CDCl_3$): (ppm)
1.3-1.8 (m, 10H), 2.25 (t, 1H), 2.42 (m, 2H), 2.77 (m, 1H), 2.97 (m, 2H), 3.26 (m, 3H), 3.49 (m, 1H), 3.72 (m, 1H), 7.18 (m, 2H), 7.51 (br, 2H)
MS (FAB+): m/z 334 (MH^+)

(Compound 30) Purified by silica gel column chromatography (methanol:methylene chloride = 1:5), oil, yield: 69%.
^{1}H-NMR ($CDCl_3$): (ppm)
1.45 (m, 8H), 1.66 (m, 6H), 2.01 (m, 1H), 2.34 (m, 1H), 2.52 (m, 1H), 2.77 (m, 2H), 3.11 (m, 1H), 3.19 (t, 2H), 3.88 (m, 1H), 4.00 (m, 1H), 7.19 (m, 2H), 7.52 (br, 2H)
MS (FAB+): m/z 348 (MH^+)

(Compound 31) Purified by silica gel column chromatography (methanol:methylene chloride = 1:5), oil, yield: 98%.
^{1}H-NMR ($CDCl_3$): (ppm)
1.4-1.7 (m, 8H), 1.76 (m, 4H), 2.33 (m, 3H), 2.40 (m, 2H), 3.30 (m, 2H), 3.86 (m, 1H), 7.19 (m, 2H), 7.51 (br, 2H), 10.1 (br, 1H)
MS (FAB+): m/z 320 (MH^+)

(Compound 32) Crystallized from water-containing acetonitrile, yield: 89%.
^{1}H-NMR ($CDCl_3$): (ppm)
0.92 (d, 3H), 1.27 (m, 5H), 1.36 (m, 3H) 1.53 (m, 2H), 1.9-1.9 (m, 7H), 1.99 (t, 2H), 2.36

(dd, 2H), 2.99 (d, 2H), 3.32 (t, 2H), 7.19 (m, 2H), 7.51 (br, 2H), 10.2 (br, 1H)
MS (FAB$^+$): m/z 360 (MH$^+$)

(Compound 36) Crystallized from water-containing acetonitrile, yield: 80%.
^{1}H-NMR ($CDCl_3$): (ppm)
1.52 (m, 2H), 1.6-1.9 (m, 4H), 2.53 (t, 2H), 2.75 (t, 2H), 2.91 (t, 2H), 3.33 (t, 2H), 3.64 (s, 2H), 7.0-7.2 (m, 7H), 7.5 (br, 1H), 9.8 (br, 1H)
MS (FAB$^+$): m/z 352 (MH$^+$)

Example 3: Synthesis of 1-(5-(2-benzimidazoylthio)pentyl)-4-cyano-4-phenylpiperidine (Compound 39)

To 0.3 g of 5-(2-benzimidazoylthio)pentyl bromide and 0.23 g of 4-cyano-4-phenylpiperidine, 2.5 ml of acetonitrile and 0.17 ml of triethylamine were added and the mixture was refluxed under heating for 16 hours. After cooling, the mixture was added with water and extracted with ethyl acetate. The organic layer was washed with wafer and dried over sodium sulfate, and then the solvent was evaporated under reduced pressure (0.35 g). The residue was purified by silica gel chromatography (methanol:methylene chloride = 1:10) and crystallized from water-containing acetonitrile to obtain 0.29 g of the target title substance (yield: 76%).
^{1}H-NMR ($CDCl_3$): (ppm)
1.52 (m, 4H), 1.81 (m, 2H), 2.10 (m, 4H), 2.45 (m, 4H), 3.02 (m, 2H), 3.35 (t, 2H), 7.19 (m, 2H), 7.36 (m, 4H), 7.49 (m, 2H), 7.66 (br, 1H), 9.7 (br, 1H)
MS (FAB$^+$): m/z 405 (MH$^+$)

The following compounds were synthesized in the same manner as in Example 3 by changing the starting material. When crystals were not deposited in the reaction system, water was added and extracted with ethyl acetate, then the organic layer was washed with water and dried over sodium sulfate, and the solvent was evaporated under reduced pressure. Procedure thereafter is specified in the explanation for each compound.

(Compound 37) Crystallized from water-containing acetonitrile, yield: 66%.
^{1}H-NMR ($CDCl_3$): (ppm)

1.52 (m, 2H), 1.65 (m, 2H), 2.48 (dd, 2H), 2.59 (m, 2H), 2.72 (t, 2H), 3.17 (m, 2H), 3.34 (t, 2H), 6.07 (t, 1H), 7.1-7.4 (m, 8H), 7.68 (br, 1H), 9.6 (br, 1H)
MS (FAB$^+$): m/z 378 (MH$^+$)

(Compound 38) Purified by silica gel column chromatography (ethyl acetate:methylene chloride = 1:10), oil, yield: 78%.
^{1}H-NMR ($CDCl_3$): (ppm)
1.51 (m, 2H), 1.63 (m, 2H), 1.80 (m, 2H), 2.58 (t, 2H), 2.84 (m, 2H), 2.90 (m, 2H), 3.32 (t, 2H), 3.60 (s, 2H), 6.73 (d, 1H), 7.09 (d, 1H), 7.16 (m, 2H), 7.42 (br, 2H)
MS (FAB$^+$): m/z 358 (MH$^+$)

(Compound 40) Purified by silica gel column chromatography (methanol:methylene chloride = 1:10), oil, yield: 94%.
^{1}H-NMR ($CDCl_3$): (ppm)
1.43 (m, 2H), 1.52 (m, 2H), 1.76 (m, 2H), 1.91 (s, 3H), 2.11 (d, 2H), 2.29 (m, 4H), 2.46 (dd, 2H), 2.78 (m, 2H), 3.30 (t, 2H), 7.18 (m, 2H), 7.29 (m, 5H), 7.59 (br, 2H), 10.15 (br, 1H)
MS (FAB$^+$): m/z 422 (MH$^+$)

(Compound 41) Purified by silica gel column chromatography (methanol:methylene chloride =1:10) and then crystallized from water-containing acetonitrile, yield: 68%.
^{1}H-NMR ($CDCl_3$): (ppm)
1.50 (m, 2H), 1.61 (m, 2H), 1.80 (m, 4H), 2.26 (m, 3H), 2.47 (m, 2H), 2.56 (m, 2H), 3.33 (t, 2H), 7.17 (m, 2H), 7.26 (m, 2H), 7.35 (m, 2H), 7.49 (m, 4H), 10.1 (br, 1H)
MS (FAB$^+$): m/z 396 (MH$^+$)

(Compound 42) Purified by silica gel column chromatography (methanol:methylene chloride = 1:10), oil, yield: 54%.
^{1}H-NMR ($CDCl_3$): (ppm)
1.73 (m, 2H), 1.83 (m, 2H), 2.15 (m, 4H), 2.52 (m, 4H), 3.05 (d, 2H), 3.36 (t, 2H), 7.19 (m, 2H), 7.36 (m, 4H), 7.46 (m, 3H), 9.7 (br, 1H)
MS (FAB$^+$): m/z 391 (MH$^+$)

(Compound 43) Purified by silica gel column chromatography (methanol:methylene chloride = 1:10), oil, yield: 72%.

^{1}H-NMR ($CDCl_3$): (ppm)

1.28 (m, 2H), 1.50 (m, 4H), 1.77 (m, 2H), 2.11 (m, 4H), 2.45 (m, 4H), 3.17 (d, 2H), 3.34 (t, 2H), 7.18 (m, 2H), 7.36 (m, 4H), 7.48 (m, 2H), 7.65 (br, 1H), 9.6 (br, 1H)

MS (FAB^+): m/z 419 (MH^+)

(Compound 44) Purified by silica gel column chromatography (methanol:methylene chloride = 1:10) and then crystallized from water-containing acetonitrile, yield: 52%.

^{1}H-NMR ($CDCl_3$): (ppm)

1.29 (m, 6H), 1.43 (m, 2H), 1.73 (m, 2H), 1.76 (m, 2H), 2.13 (m, 4H), 2.48 (m, 4H), 3.20 (d, 2H), 3.33 (t, 2H), 7.19 (m, 2H), 7.36 (m, 4H), 7.49 (m, 2H), 7.67 (br, 1H), 9.8 (br, 1H)

MS (FAB^+): m/z 447 (MH^+)

(Compound 45) Crystallized from water-containing acetonitrile, yield: 67%.

^{1}H-NMR ($CDCl_3$): (ppm)

1.48 (m, 2H), 1.58 (m, 2H), 1.76 (m, 4H), 2.15 (dt, 2H), 2.42 (m, 4H), 2.86 (d, 2H), 3.33 (t, 2H), 7.19 (m, 2H), 7.27 (m, 2H), 7.41 (m, 2H), 7.60 (br, 2H), 10.05 (br, 1H)

MS (FAB^+): m/z 431 (MH^+)

(Compound 46) Extracted with ethyl acetate and then crystallized form ethyl acetate/hexane, yield: 68%.

^{1}H-NMR ($CDCl_3$): (ppm)

1.34 (m, 2H), 1.50 (m, 4H), 1.76 (m, 5H), 2.18 (dt, 2H), 2.41 (m, 4H), 2.85 (d, 2H), 3.32 (t, 2H), 7.18 (m, 2H), 7.26 (m, 1H), 7.33 (m, 2H), 7.49 (m, 2H), 7.54 (br, 2H), 9.95 (br, 1H)

MS (FAB^+): m/z 410 (MH^+)

(Compound 47) Purified by silica gel column chromatography (methanol:methylene chloride = 1:10), solid, yield: 45%.

^{1}H-NMR ($CDCl_3$): (ppm)

1.6-1.9 (m, 7H), 2.21 (dt, 2H), 2.53 (m, 4H), 2.89 (d, 2H), 3.33 (t, 2H), 7.18 (m, 2H), 7.26 (m, 1H), 7.35 (m, 2H), 7.49 (m, 4H), 9.9 (br, 1H)

MS (FAB^+): m/z 382 (MH^+)

(Compound 48) Purified by silica gel column chromatography (methanol:methylene chloride = 1:10), solid, yield: 73%.

^{1}H-NMR ($CDCl_3$): (ppm)

1.44 (m, 2H), 1.63 (m, 4H), 1.76 (m, 5H), 2.34 (m, 4H), 2.71 (d, 2H), 2.75 (s, 2H), 3.33 (t, 2H), 7.19 (m, 4H), 7.28 (m, 3H), 7.50 (br, 2H), 10.05 (br, 1H)

MS (FAB$^+$): m/z 410 (MH^+)

(Compound 49) Purified by silica gel column chromatography (methanol:methylene chloride = 1:10), oil, yield: 78%.

^{1}H-NMR ($CDCl_3$): (ppm) 7.27

1.47 (m, 2H), 1.61 (m, 2H), 1.78 (M, 2H), 2.04 (m, 4H), 2.42 (m, 4H), 2.80 (d, 2H), 2.97 (s, 3H), 3.32 (t, 2H), 7.18 (m, 2H), 7.27 (m, 1H), 7.37 (m, 4H), 7.50 (br, 2H), 10.1 (br, 1H)

MS (FAB$^+$): m/z 410 (MH^+)

Example 4: Synthesis of ethyl 4-(2-benzimidazolylthio)valerate

11 g of 2-mercaptobenzimidazole and 14.6 g of 5-bromovaleric acid were dissolved in 50 ml of ethanol and the mixture was refluxed under heating for 24 hours. After cooling, the mixture was added with wafer and adjusted to pH 8 with aqueous sodium hydroxide. The deposited crystals were collected by filtration and washed with water-containing methanol to obtain 16.9 g of the title compound (yield: 83%).

Example 5: Synthesis of 4-(4-(2-benzimidazolylthio)valeroyl)morpholine (Compound 4)

0.56 g of ethyl 4-(2-benzimidazolylthio)valerate and 0.53 g of morpholine were heated at 100°C for 20 hours. The reaction mixture was applied without treatment to a silica gel column for purification (methanol:methylene chloride = 1:10), and 0.37 g of the title compound was obtained as solid (yield: 58%).

^{1}H-NMR ($CDCl_3$): (ppm) 1.83 (m, 4H), 2.40 (t, 2H), 3.26 (t, 2H), 3.44 (t, 2H), 3.66 (m, 6H), 7.19 (m, 2H), 7.41 (br, 1H), 7.64 (br, 1H), 10.82 (br, 1H)

MS (FAB$^+$): m/z 320 (MH^+)

Example 6: Synthesis of 4-(5-(1-propylbenzimidazolyl-2-thio)pentyl)morpholine (Compound 6)

0.24 g of 4-(5-(benzimidazolyl-2-thio)pentyl)morpholine was dissolved in 1.5 ml of dimethylformamide (DMF), added with 0.33 g of potassium carbonate and 0.16 g of propyl iodide, and stirred at 50°C for 10 hours. The reaction mixture was added with water and extracted with ethyl acetate, and the solvent was evaporated under reduced pressure. The residue was purified by using a silica gel column (methanol:methylene chloride = 1:10) to obtain 0.23 g of the title compound as oil (yield: 83%).

^{1}H-NMR ($CDCl_3$): (ppm)

0.97 (t, 3H), 1.53 (m, 4H), 1.84 (m, 4H), 2.35 (t, 2H), 2.44 (m, 4H), 3.40 (t, 2H), 3.71 (m, 4H), 4.06 (t, 2H), 7.19 (m, 2H), 7.24 (m, 1H), 7.66 (m, 1H)

MS (FAB$^+$): m/z 348 (MH^+)

Example 7: Synthesis of 4-(5-(1-propionylbenzimidazolyl-2-thio)pentyl)morpholine (Compound 7)

0.24 g of 4-(5-(benzimidazolyl-2-thio)pentyl)morpholine was dissolved in 1 ml of dimethylacetamide and 2 ml of acetonitrile, added with 0.17 ml of triethylamine and then with 0.08 ml of propionyl chloride, and stirred at 50°C for 2 hours. The reaction mixture was added with water and extracted with ethyl acetate, and then the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (methanol:methylene chloride = 1:10) to obtain 0.27 g of the title compound as oil (yield: 93%).

^{1}H-NMR ($CDCl_3$): (ppm)

1.36 (t, 3H), 1.55 (m, 4H), 1.82 (m, 2H), 2.37 (t, 2H), 2.47 (m, 4H), 3.09 (q, 2H), 3.34 (t, 2H), 3.73 (m, 4H), 7.2 (m, 2H), 7.65 (m, 2H)

MS (FAB$^+$): m/z 362 (MH^+)

Example 8: Synthesis of 1-(4-bromovaleroyl)-4-methylpiperidine

1.09 g of 4-methylpiperidine was dissolved in 10 ml of acetonitrile and added dropwise with 1.09 g of 4-bromovaleroyl chloride. The reaction mixture was stirred for 2 hours, then poured into water and extracted with ethyl acetate. The organic layer was washed with wafer and dried over sodium sulfate, and then the solvent was evaporated under reduced pressure to obtain 1.07 g of the title compound (yield: 82%).

Example 9: Synthesis of 1-(4-(2-benzimidazolylthio)valeroyl)-4-methylpiperidine

(Compound 12)

0.15 g of 2-mercaptobenzimidazole and 0.26 g of 1-(4-bromovaleroyl)-4-methylpiperidin were suspended in acetonitrile, and the suspension was added with 0.17 ml of triethylamine and refluxed for 7 hours. The reaction mixture was added with water and extracted with ethyl acetate. The organic layer was washed with water and dried over sodium sulfate, and then the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (methanol:methylene chloride = 1:10) to obtain 0.07 g of the title compound as oil (yield: 21%).

^{1}H-NMR ($CDCl_3$): (ppm)

0.86 (d, 3H), 1.00 (m, 2H), 1.57 (m, 3H), 1.74 (m, 4H), 2.30 (m, 2H), 2.49 (t, 1H), 2.89 (t, 1H), 3.18 (m, 2H), 3.69 (d, 1H), 4.56 (d, 1H), 7.08 (m, 2H), 7.44 (br, 2H), 11.5 (br, 1H)

MS (FAB$^+$): m/z 320 (MH^+)

Example 10: Synthesis of 2-(2-(2-chloroethoxy)ethylthiobenzimidazole)

6.0 g of 2-mercaptobenzimidazole and 23 g of bis(2-chloroethyl) ether were dissolved in 45 ml of ethanol, and the mixture was added with 0.6 ml of triethylamine and refluxed for 15 hours. After the ethanol was evaporated under reduced pressure, the precipitates were added with 80 ml of ethyl acetate/hexane (1:1) for washing. The residue was dissolved in 20 ml of methanol and neutralized with aqueous sodium hydroxide. The deposited crystals were collected by filtration, washed with water/methanol (1:1) and dried to obtain 6.5 g of the title compound.

MS (FAB$^+$): m/z 257 (MH^+)

Example 11: Synthesis of 2-(2-(2-(2-chloroethoxy)ethoxy)ethylthiobenzimidazole)

12.0 g of 2-mercaptobenzimidazole and 60 g of bis(2-chloroethoxy)ethane were dissolved in 70 ml of ethanol, and the mixture was added with 1.0 ml of triethylamine and refluxed for 15 hours. After the ethanol was evaporated under reduced pressure, the precipitates were added with 80 ml of ethyl acetate/hexane (1:1) for washing. The residue was dissolved in 20 ml of methanol and neutralized with aqueous sodium hydroxide. The deposited oil was extracted with ethyl acetate and the organic layer was washed with water and dried over sodium sulfate. Then, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column

chromatography (methylene chloride) to obtain 16 g of the title compound as solid.
MS (FAB$^+$): m/z 285 (MH$^+$)

Example 12: Synthesis of 4-(2-(2-benzimidazoyl-2-thio)ethoxy)ethylmorpholine (Compound 50)

0.26 g of 2-(2-(2-chloroethoxy)ethylthiobenzimidazole and 0.19 g of morpholine were added to 2.5 ml of acetonitrile, and the mixture was refluxed under heating for 19 hours. After cooling, the reaction mixture was added with water and extracted with ethyl acetate. The organic layer was washed with water and dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate:methylene chloride = 1:2) to obtain 0.23 g of title compound (yield: 75%).
^{1}H-NMR ($CDCl_3$): (ppm)
2.60 (t, 4H), 2.71 (t, 2H), 3.28 (t, 2H), 3.67 (t, 4H), 3.73 (t, 2H), 3.83 (t, 2H), 7.21 (m, 2H), 7.49 (m, 3H)
MS (FAB$^+$): m/z 308 (MH$^+$)

The following compounds were synthesized in the same manner as in Example 12.

(Compound 51) Purified by silica gel column chromatography (methanol:methylene chloride = 1:10), oil, yield: 70%.
^{1}H-NMR ($CDCl_3$): (ppm)
2.50 (m, 4H), 2.59 (t, 2H), 3.33 (t, 2H), 3.68 (m, 8H), 3.82 (t, 2H), 7.19 (m, 2H), 7.52 (br, 2H), 11.2 (br, 1H)
MS (FAB$^+$): m/z 352 (MH$^+$)

(Compound 52) Purified by silica gel column chromatography (methanol:methylene chloride = 1:10), oil, yield: 82%
^{1}H-NMR ($CDCl_3$): (ppm)
0.83 (d, 3H), 1.26 (m, 2H), 1.38 (m, 1H), 1.63 (d2H), 2.05 (t, 2H), 2.67 (t, 2H), 3.08 (d, 2H), 3.21 (t, 2H), 3.70 (t, 2H), 3.78 (t, 2H), 7.21 (m, 2H), 7.52 (br, 2H), 11.7 (br, 1H)
MS (FAB$^+$): m/z 320 (MH$^+$)

(Compound 53) Purified by silica gel column chromatography (methanol:methylene chloride = 1:10), oil, yield: 85%

^{1}H-NMR ($CDCl_3$): (ppm)

0.88 (d, 3H), 1.26 (m, 2H), 1.35 (m, 1H), 1.60 (d, 2H), 2.00 (t, 2H), 2.59 (t, 2H), 2.97 (d, 2H), 3.33 (t, 2H), 3.68 (t, 2H), 3.78 (t, 2H), 7.19 (m, 2H), 7.52 (br, 2H), 11.8 (br, 1H)

MS (FAB^+): m/z 364 (MH^+)

(Compound 54) Purified by silica gel column chromatography (methanol:methylene chloride = 1:10), oil, yield: 81%

^{1}H-NMR ($CDCl_3$): (ppm)

1.96 (m, 4H), 2.60 (dt, 2H), 2.84 (t, 2H), 3.15 (d, 2H), 3.30 (t, 2H), 3.78 (t, 2H), 3.86 (t, 2H), 7.10 (m, 2H), 7.20 (m, 2H), 7.24 (m, 2H), 7.60 (m, 3H), 11.1 (br, 1H)

MS (FAB^+): m/z 407 (MH^+)

Example 13: Synthesis of 1-(5-(benzimidazoyl-2-oxy)pentyl)-4-cyano-4-phenyl-piperidine (Compound 55)

Example 13a: Synthesis of 2-(5-hydroxy-pentyloxy)-1-isopropenylbenzimidazole

3.3 g of 1,5-pentanediol and 0.4 g of sodium were stirred under nitrogen atmosphere for 30 minutes with heating. After the sodium disappeared, the reaction mixture was added dropwise with 30 ml of anhydrous THF containing 2.9 g of 2-chloro-1-isopropenylbenzimidazole and then refluxed for 8 hours. After cooling to room temperature, the mixture was added with water and extracted with ethyl acetate. The solvent was evaporated under reduced pressure and the resulting residue was purified by silica gel column chromatography (ethyl acetate) to obtain 2 g of the title compounds (yield: 51%).

Example 13b: Synthesis of 2-(5-bromo-pentyloxy)-1-isopropenylbenzimidazole

A solution of 1.06 g of the compound obtained in Example 13a in 20 ml of dichloromethane was added with 1.8 g of carbon tetrabromide and 1.4 g of triphenylphosphine and stirred for 1 hour. The reaction mixture was added with saturated aqueous NaOH for washing. The solvent was evaporated under reduced pressure and the resulting residue was purified by silica gel column chromatography

(ethyl acetate) to obtain 1.2 g of the title compound (yield: 91%).

Example 13c: Synthesis of 2-(5-bromo-pentyloxy)benzimidazole

1.2 g of the compound obtained in Example 13b was dissolved in 10 ml of tBuOH, slowly added dropwise with 30 ml of a mixed solution of $KMnO_4$ (1.92 g) and 50 ml of 0.1 N NaOH, and stirred for 1 hour. The reaction mixture was extracted three times with chloroform. The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography (ethyl acetate) to obtain 0.45 g of the title compound (yield: 43%).

Example 13d: Synthesis of 1-(5-(benzimidazoyl-2-oxy)pentyl)-4-cyano-4-phenyl-piperidine (Compound 55)

283 mg of the compound obtained in Example 13c and 223 mg of 4-cyano-4-phenylpiperidine were refluxed in 10 ml of acetonitrile as a solvent containing 120 mg of triethylamine for 4.5 hours. After cooling to room temperature, the reaction mixture was extracted with ethyl acetate. The solvent was evaporated under reduced pressure and the resulting residue was purified by silica gel column chromatography (ethyl acetate) to obtain 170 mg of the title compound (yield: 44%).

^{1}H-NMR ($CDCl_3$): (ppm)

1.50 (m, 2H), 1.62 (m, 2H), 1.87 (m, 2H), 2.12 (m, 4H), 2.48 (m, 4H), 3.06 (m, 2H), 4.53 (t, 2H), 7.07-7.60 (m, 9H)

MS (FAB^-): m/z 387 (M-H)

In the same manner as in Example 13, (Compound 56) was obtained (yield: 43%).

^{1}H-NMR ($CDCl_3$): (ppm)

1.49 (m, 2H), 1.65 (m, 2H), 1.83 (m, 4H), 2.20 (m, 2H), 2.48 (m, 4H), 2.87 (m, 2H), 4.54 (t, 2H), 7.12-7.52 (m, 9H)

MS (FAB^+): m/z 380 (MH^+)

Example 14: Synthesis of 2-(5-(4-morpholino))-5-methylbenzimidazole (Compound 9)

Example 14a: Synthesis of 2-(5-hydroxypentylthio)-5-methylbenzimidazole

2.46 g of 5-methyl-2-mercaptobenzimidazole and 3.4 g of 5-bromopentyl

acetate were dissolved in 30 ml of ethanol and the mixture was refluxed with stirring under heating for 7 hours. After cooling to room temperature, the reaction mixture was added with was 22.5 ml of 2 N sodium hydroxide solution and stirred at room temperature for 1 hour, and then poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over sodium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride:methanol = 95:5) to obtain 3.04 g of the title compound as pale yellow oil (yield: 81%).

Example 14b: Synthesis of 2-(5-bromopentylthio)-5-methylbenzimidazole

1.4 g of the compound obtained in Example 14a and 2.8 g of carbon tetrabromide were added to 15 ml of tetrahydrofuran and then gradually added with 2.2 g of triphenylphosphine. After the reaction mixture was stirred at room temperature for 1 hour, the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 4:1 to 2:2) to obtain 1.18 g of the title compound as yellow crystals (yield: 67%).

Example 14c: Synthesis of 2-(5-(4-morpholino))-5-methylbenzimidazole (Compound 9)

0.31 g of the compound obtained in Example 14b and 0.19 g of morpholine were added to 5 ml of acetonitrile and the mixture was refluxed with stirring under heating for 8 hours. After cooling to room temperature, the reaction mixture was poured into 100 ml of saturated aqueous sodium hydrogencarbonate and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (methylene chloride:methanol = 9:1) to obtain 0.22 g of the title compound as pale yellow oil (yield: 77.0%).

^{1}H-NMR ($CDCl_3$): (ppm)

1.5-1.52 (m, 4H), 1.74 (q, 2H), 2.29 (t, 2H), 2.39-2.45 (m, 7H), 3.27 (t, 2H), 3.72 (t, 4H), 6.98 (d, 1H), 7.26 (br, 1H), 7.38 (br, 1H)

MS (FAB^+): m/z 320 (MH^+)

Example 15: Synthesis of 2-(5-(4-morpholino))-5-methoxybenzimidazole (Compound 19)

Synthesis was performed in the same manner as in Example 14 by using 5-methoxy-2-mercaptobenzimidazole as the starting material. The product was purified by silica gel chromatography (methylene chloride:methanol = 9:1) to obtain the title compound as colorless oil (yield: 82%).

^{1}H-NMR ($CDCl_3$): (ppm)

1.32-1.52 (m, 4H), 1.76 (q, 2H), 2.28 (t, 2H), 2.40-2.48 (m, 4H), 3.26 (t, 2H), 3.70 (t, 4H), 6.80 (d, 1H), 6.98 (br, 1H), 7.38 (br, 1H)

MS (FAB^+): m/z 335 (MH^+)

Example 16: Synthesis of 2-(5-(4-morpholino))-5-chlorobenzimidazole (Compound 20)

Synthesis was performed in the same manner as in Example 14 by using 5-chloro-2-mercaptobenzimidazole as the starting material. The product was purified by silica gel chromatography (methylene chloride:methanol = 9:1) to obtain the title compound as pale yellow oil (yield: 88%).

^{1}H-NMR ($CDCl_3$) (ppm)

1.32-1.50 (m, 4H), 1.74 (q, 2H), 2.28 (t, 2H), 2.38-2.45 (m, 4H), 3.25 (t, 2H), 3.70 (t, 4H), 3.80 (s, 3H), 6.80 (d, 1H), 6.98 (br, 1H), 7.38 (br, 1H)

MS (FAB^+): m/z 340 (MH^+)

Example 17: Synthesis of 1-(5-(4-benzimidazolyl-2-thio)valeryl)-1,2,3,4-tetrahydroquinoline (Compound 33)

1.0 g of 1-(5-benzimidazolyl-2-thio)valeric acid and 0.53 g of 1,2,3,4-tetrahydroquinoline were added to a mixed solvent of 5 ml of methylene chloride and 10 ml of pyridine and the mixture was stirred on an ice bath. The mixture was added with 0.92 g of WSC and then stirred at room temperature for 4 hours. The mixture was poured into 150 ml of saturated aqueous sodium hydrogencarbonate and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over sodium sulfate, and then the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (methylene chloride:methanol = 9:1) to obtain 0.9 g of the title compound as white crystals (yield: 62%).

^{1}H-NMR ($CDCl_3$): (ppm)

1.70-2.00 (m, 6H), 2.68 (t, 2H), 2.68-2.73 (m, 2H), 3.20 (t, 2H), 3.80 (t, 2H), 7.06-7.20 (m,

6H), 7.39-7.59 (br, 2H)

MS (FAB+): m/z 366 (MH^+)

Example 18: Synthesis of 1-(5-benzimidazolyl-2-thio)pentyl-1,2,3,4-tetrahydroquinoline (Compound 34)

73 mg of the compound obtained in Example 17 was added to 2 ml of tetrahydrofuran and stirred on an ice bath. The mixture was added with 0.6 ml of 1 M borane/tetrahydrofuran complex, and the mixture was reacted overnight at room temperature, then added with 1 ml of 4 N hydrochloric acid solution in dioxane and refluxed under heating for 1 hour. After cooling to room temperature, the reaction mixture was poured into 10 ml of saturated aqueous sodium hydrogencarbonate and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over sodium sulfate, and then the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 3.5:1) to obtain 8 mg of the title compound as colorless oil (yield: 12%).

^{1}H-NMR ($CDCl_3$): (ppm)

1.38-1.50 (m, 2H), 1.52-1.62 (m, 2H), 1.75-1.84 (m, 2H), 1.86-1.95 (m, 2H), 2.70 (t, 2H), 3.15-3.24 (m, 4H), 3.30 (t, 2H), 6.47-6.58 (m, 2H), 6.92 (d, 1H), 7.00 (dd, 1H), 7.15-7.22 (m, 2H), 7.48 (br, 2H)

MS (FAB+): m/z 351 (MH^+)

In the same manner as in Example 17, (Compound 35) was synthesized.

^{1}H-NMR ($CDCl_3$): (ppm)

1.87 (m, 4H), 2.66 (br, 2H), 3.31 (t, 2H), 3.95 (br, 2H), 4.29 (t, 2H), 6.91 (m, 2H), 7.10 (m, 2H), 7.21 (m, 2H), 7.51 (br, 2H)

MS (FAB+): m/z 368 (MH^+)

Example 19: Synthesis of 2-(6-(1-(4-hydroxy-4-phenyl)piperidino)heptyl)-1H-benzimidazole (Compound 58)

Example 19a: Synthesis of 2-(6-hydroxyheptyl)-1H-benzimidazole

3.28 g of methyl 6-hydroxyheptanoate and 2.16 g of phenylenediamine were dissolved in a mixed solvent of 10 ml of concentrated hydrochloric acid and 20 ml of

water, and the mixture was refluxed with stirring under heating for 24 hours. After cooling to room temperature, the reaction mixture was adjusted to pH 8 with about 100 ml of 1 N sodium hydroxide solution and saturated aqueous sodium hydrogencarbonate. The reaction mixture was extracted three times with 150 ml of ethyl acetate, and the organic layer was washed with saturated brine and dried over sodium sulfate. After the solvent was evaporated under reduced pressure, the residue was purified by silica gel column chromatography (ethyl acetate - ethyl acetate:methanol = 95:5) to obtain 3.03 g of the title compound as pale brown solid (yield: 70%).

Example 19b: Synthesis of 2-(6-bromoheptyl)-1H-benzimidazole

2.18 g of the compound obtained in Example 19a, 4.97g of carbon tetrabromide and 3.93 g of triphenylphosphine were added to 30 ml of tetrahydrofuran and the mixture was reacted overnight at room temperature. After the reaction was completed, the solvent was evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate:hexane = 1:1) to obtain 2.10 g of the title compound as pale yellow solid (yield: 75%).

Example 19c: Synthesis of 2-(6-(1-(4-hydroxy-4-phenyl)piperidino)heptyl)-1H-benzimidazole (Compound 58)

0.28 g of the compound obtained in Example 19b and 0.21 g of 4-hydroxy-4-phenylpiperidine were added to 2.5 ml of acetonitrile and the mixture was refluxed with stirring under heating for 8 hours. After cooling to room temperature, the reaction mixture was poured into 50 ml of saturated aqueous sodium hydrogencarbonate and extracted with 50 ml of ethyl acetate. The ethyl acetate layer was washed with saturated brine and dried over sodium sulfate. After the solvent was evaporated under reduced pressure, the residue was purified by silica gel column chromatography (methylene chloride:methanol =9:1 → 5:1) to obtain 0.24 g of the title compound as white crystals (yield: 64%).

^{1}H-NMR ($CDCl_3$+CD_3OD): (ppm)

1.30-1.55 (m, 4H), 1.70-1.85 (m, 4H), 2.07-2.20 (m, 2H), 2.30-2.55 (m, 4H), 2.70-2.95 (m, 6H), 7.10-7.40 (m, 5H), 7.42-7.58 (m, 2H)

MS (FAB$^+$): m/z 378 (MH^+)

Example 20: Synthesis of 2-(6-(1-(4-cyano-4-phenyl)piperidino)heptyl)-1H-benzimidazole (Compound 57)

Synthesis was performed in the same manner as in Example 19 by using the compound obtained in Example 19b and 4-cyano-4-phenylpiperidine. The product was purified by silica gel chromatography (methylene chloride:methanol = 9:1) and crystallized from ethyl acetate/hexane (yield: 54%).

^{1}H-NMR ($CDCl_3$): (ppm)

1.30-1.55 (m, 6H), 1.90 (q, 2H), 2.06-2.15 (m, 4H), 2.34-2.49 (m, 4H), 2.90-3.04 (m, 4H), 7.17-7.24 (m, 2H), 7.30-7.42 (m, 3H), 7.45-7.60 (m, 4H)

MS (FAB^+): m/z 387 (MH^+)

Test Example 1

Activity of the compounds of the present invention for suppressing the foaming of macrophages, which triggers arterial sclerosis, was examined.

(1) In vitro experiment using mouse peritoneal macrophages.

15-Week old female ICR mice (Nippon SLC) were subjected to bleeding by cutting off their cervicalis, and Hanks buffer (Nippon Seiyaku) was injected into their peritoneal cavities. After abdominal regions of the mice were massaged, the buffer was recovered immediately, and then the resulting buffer was centrifuged at 1,000 r.p.m. for five minutes to collect peritoneal macrophages. Then, the collected macrophages were suspended in GTI medium (Wako Pure Chemical Industries), and inoculated onto a 24-well microtiter plate. After the macrophages were cultivated at 37℃ under 5% CO_2 for two hours, the culture medium was changed with Dulbecco Modified Eagle Medium (MEM, Nippon Seiyaku). The macrophages were further cultivated at 37℃ under 5% CO_2 for 16 hours, and then a test compound and liposomes were added to the culture.

1) Test compound: dissolved in DMSO (Wako Pure Chemical Industries),

2) Liposomes: PC/PS/DCP/CHOL = 50/50/10/75 (nmol)

PC: Phosphatidylcholine (Funakoshi);

PS: Phosphatidylserine (Funakoshi);

DCP: Dicetylphosphate (Funakoshi);

CHOL: Cholesterol (Sigma)

After cultivation was further continued at 37℃ under 5% CO_2 for 16 hours,

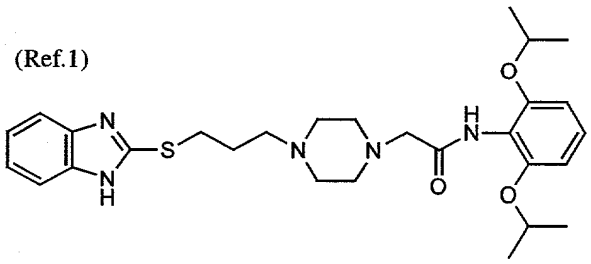
lipid fraction was extracted with chloroform and methanol. The extracted lipid fraction was dissolved in isopropyl alcohol, and the produced cholesterol ester (CE) was quantified by an enzymatic luminescence method. Yield of the cholesterol ester was calculated as a relative ratio based on yield of the control as 100% where no test compound was added.

Compound	Dose	CE yield (%)
(1)	5 μM	22
(2)	5 μM	18
(3)	5 μM	8.2
(4)	5 μM	16
(5)	5 μM	21
(6)	5 μM	27
(7)	5 μM	22
(8)	5 μM	23
(9)	5 μM	21
(10)	5 μM	12
(11)	5 μM	12
(12)	5 μM	24
(13)	5 μM	12
(14)	5 μM	22
(15)	5 μM	23
(16)	5 μM	12
(17)	5 μM	23
(18)	5 μM	22
(19)	5 μM	24
(20)	5 μM	25
(21)	5 μM	14
(22)	5 μM	19
(23)	5 μM	12
(24)	5 μM	18
(25)	5 μM	14
(26)	5 μM	23

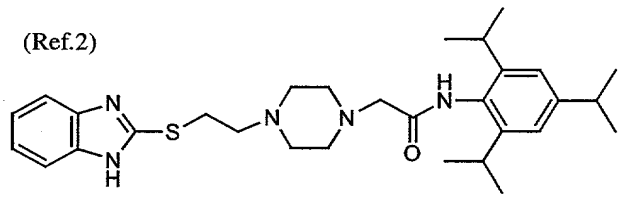
(27)	5 μM	15
(28)	5 μM	4.2
(29)	5 μM	18
(30)	5 μM	19
(31)	5 μM	21
(32)	5 μM	18
(33)	5 μM	18
(34)	5 μM	21
(35)	5 μM	22
(36)	5 μM	18
(37)	5 μM	20
(38)	5 μM	18
(39)	5 μM	4.1
(40)	5 μM	8.2
(41)	5 μM	4.2
(42)	5 μM	18
(43)	5 μM	16
(44)	5 μM	7.5
(45)	5 μM	23
(46)	5 μM	18
(47)	5 μM	15
(48)	5 μM	21
(49)	5 μM	22
(50)	5 μM	4.6
(51)	5 μM	23
(52)	5 μM	10
(53)	5 μM	22
(54)	5 μM	21
(55)	5 μM	21
(56)	5 μM	18
(57)	5 μM	22
(58)	5 μM	20
(Ref. 1)	5 μM	95

(Ref. 2)	5 μM	98
(Ref. 3)	5 μM	78
(Ref. 4)	5 μM	89
(Ref. 5)	5 μM	102

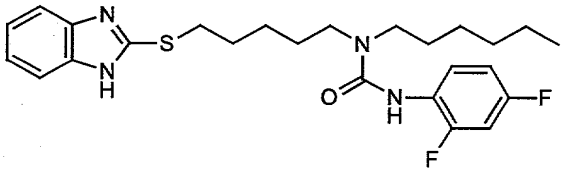
(Ref.1)



(Ref.2)



(Ref.3)



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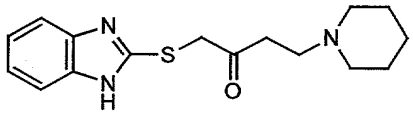
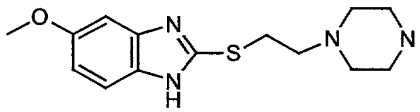


(Ref.5)



(Ref. 1) Compound (9) described in International Patent Publication WO98/54153

(Ref. 2) Compound (49) described in International Patent Publication WO98/54163

(Ref. 3) Compound (3) described in Bio. Med. Chem. Lett., Vol. 5(2), 167-172 (1995)

(Ref. 4) A synthesis intermediate described in Chim. Chronika., Vol. 9(3), 239-246 (1980)

(Ref. 5) Compound (7) described in International Patent Publication WO95/34304

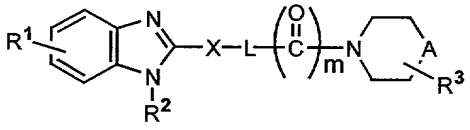
From these results, it is clearly understood that the compounds of the present invention acted on macrophases and remarkably reduced the rate of cholesterol ester synthesis (a smaller value means a more potent suppression, and 100% indicates no suppression). Whilst, the known benzimidazole derivatives used for comparison, i.e., Compounds of (Ref. 1), (Ref. 2) and (Ref.3), had a benzimidazole structure similar to that of the compounds of the present invention, however, they exerted almost no inhibitory effect on macrophages. Further, the compound described as a medicament having other efficacy (Ref. 5) and the compound described as a synthesis intermediate (Ref. 4) are structurally similar benzimidazole derivatives, however, they were completely inactive in inhibition of macrophages.

Industrial Applicability

The benzimidazole derivatives of the present invention have an action of suppressing the foaming of macrophages, and are useful as active ingredients of medicaments for preventive and/or therapeutic treatment of arteriosclerosis or medicaments for preventive and/or therapeutic treatment of hyperlipidemia. Further, they are also useful as additives for silver halide photosensitive materials or for the production of liquid crystals.

What is claimed is:

1. A benzimidazole compound represented by the following formula (I) or a salt thereof:



wherein, R^1 represents one or more functional groups on the benzene ring selected from the group consisting of hydrogen atom, a halogen atom, a lower alkyl group, and a lower alkoxy group; R^2 represents hydrogen atom, an alkyl group, or an acyl group; R^3 represents one or more functional groups on the ring containing the nitrogen atom and A; A represents O or CH_2, or CH which forms a double bond with an adjacent carbon atom; L represents a C_4-C_8 alkylene group or an ethyleneoxy linking group represented by $(CH_2CH_2O)_nCH_2CH_2$ wherein n represents 1 or 2; X represents O, S or methylene group; and m represents 0 or 1.

2. The compound or a salt thereof according to Claim 1, wherein X is O or S.

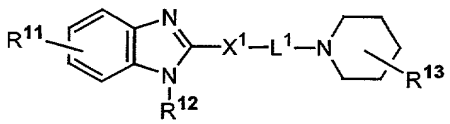
3. The compound or a salt thereof according to Claim 1 or 2, wherein m is 0.

4. The compound or a salt thereof according to any one of Claims 1 to 3, wherein each of R^1 and R^2 represents hydrogen atom.

5. The compound or a salt thereof according to any one of Claims 1 to 4, wherein L is a C_4-C_8 alkylene group.

6. The compound or a salt thereof according to any one of Claims 1 to 4, wherein L is a C_5 or C_6 alkylene group.

7. A benzimidazole compound represented by the following formula (II) or a salt thereof:



wherein, R^{11} represents one or more functional groups on the benzene ring selected

from the group consisting of hydrogen atom, a halogen atom, a lower alkyl group, and a lower alkoxy group; R^{12} represents hydrogen atom, an alkyl group, or an acyl group; R^{13} represents one or more functional groups on the piperidine ring selected from the group consisting of hydrogen atom, an alkyl group, an aryl group, hydroxy group, an alkoxy group, an amino group, an acyl group, a cyano group, a carbamoyl group and an alkoxycarbonyl group; L^1 represents a C_4-C_8 alkylene group; and X represents O, S or methylene group.

8. The compound or a salt thereof according to Claim 7, wherein L^1 is a C_4-C_8 alkylene group.

9. The compound or a salt thereof according to Claim 7 or 8, wherein R^{11} and R^{12} represent hydrogen atom.

10. The compound or a salt thereof according to any one of Claims 7 to 9, wherein R^{13} is a functional group selected from the group consisting of hydrogen atom, an alkyl group, a hydroxyalkyl group, an aryl group, hydroxy group, and cyano group.

11. The compound or a salt thereof according to any one of Claims 7 to 10, wherein L^1 is a C_5 or C_6 alkylene group.

12. A medicament comprising the compound according to any one of Claims 1 to 11 or a physiologically acceptable salt thereof as an active ingredient.

13. The medicament according to Claim 12, which is in the form of a pharmaceutical composition comprising the compound or a physiologically acceptable salt thereof as an active ingredient and a pharmaceutically additive.

14. The medicament according to Claim 12 or 13, which is used for preventive and/or therapeutic treatment of hyperlipidemia.

15. The medicament according to Claim 12 or 13, which is used for preventive and/or therapeutic treatment of arteriosclerosis.

16. The medicament according to Claim 12 or 13, which is used as an agent for suppressing foaming of a macrophage.

17. The medicament according to Claim 12 or 13, which is used as an agent for retracting arterial sclerosis lesions.

18. The medicament according to Claim 12 or 13, which is used as an agent for inhibiting formation of arterial sclerosis lesions .

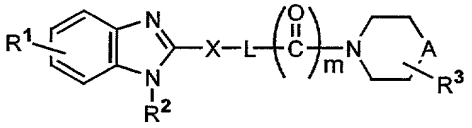
19. Use of the compound or a physiologically acceptable salt thereof according to any one of Claims 1 to 11 for manufacture of the medicament according to any one of

Claims 12 to 17.

20. A method for preventive and/or therapeutic treatment of arteriosclerosis, which comprises the step of administering a preventively and/or therapeutically effective amount of the compound according to any one of Claims 1 to 11 or a physiologically acceptable salt thereof to a mammal including human.

ABSTRACT

A benzimidazole compound or a salt thereof which has an inhibitory action of forming of macrophages and is useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of arteriosclerosis, which is represented by the formula (I):



wherein R^1 represents hydrogen atom, a halogen atom, a lower alkyl group, or a lower alkoxy group; R^2 represents hydrogen atom, an alkyl group, or an acyl group; R^3 represents a functional group on the ring; A represents O or CH_2, or CH that forms a double bond with an adjacent carbon atom; L represents a C_4-C_8 alkylene group or an ethyleneoxy linking group represented by $(CH_2CH_2O)_nCH_2CH_2$ wherein n represents 1 or 2; X represents O, S or methylene group; and m represents 0 or 1.

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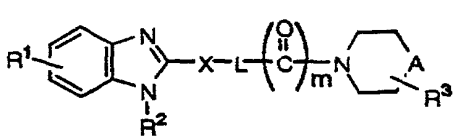
— 国際調査報告書

(54) Title: BENZIMIDAZOLE COMPOUNDS AND DRUGS CONTAINING THE SAME

(54) 発明の名称: ベンズイミダゾール化合物及びこれを含む医薬



(I)

(57) Abstract: Benzimidazole compounds of general formula (I) or salts thereof, which exhibit inhibitory activities against the conversion of macrophages into foam cells and are useful as the active ingredient of drugs to be used in the prevention and/or treatment of arteriosclerosis wherein R^1 is hydrogen, halogeno, lower alkyl, or lower alkoxy; R^2 is hydrogen, alkyl, or acyl; R^3 is a substituent on the ring; A is O or CH_2, or alternatively A represents a CH group binding to an adjacent carbon atom through a double bond; L is C_4-C_8 alkylene or an ethylene-oxy connecting group represented by the general formula: $(CH_2CH_2O)nCH_2CH_2$ (wherein n is 1 or 2); X is O, S, or methylene; and m is 0 or 1.

[続葉有]

WO 01/00588 A1

FA1551M/US

Declaration and Power of Attorney for Patent Application

特許出願宣言書および委任状

Japanese Language Declaration

私は下記発明者として以下の通り宣言します：

As a below named inventor, I hereby declare that:

私の住所、郵送先、および国籍は私の氏名の後に記載された通りです。

My residence, mailing address and citizenship are as stated next to my name.

下記名称の発明に関し請求範囲に記載され特許出願がされている発明内容につき、私が最初、最先かつ唯一の発明者（下記氏名が一つのみの場合）であるか、あるいは最初、最先かつ共同発明者（下記氏名が複数の場合）であると信じます。

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

BENZIMIDAZOLE COMPOUNDS AND MEDICAMENTS COMPRISING THE SAME

下記項目にx印が付いている場合を除き、上記発明の明細書は本書に添付されます。

the specification of which is attached hereto unless the following box is checked:

☐ 上記発明は米国出願番号あるいはPCT国際出願番号_____（確認番号_____）として_____年__月__日に出願され、_____年__月__日に補正されました（該当する場合）。

☑ was filed on June 27, 2000 as United States Application Number or PCT International Application Number PCT/JP00/04203 and was amended on _____(if applicable).

私は特許請求範囲を含み上述の補正で補正された前記明細書の内容を検討し、理解していることをここに表明します。

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

私は連邦規則法典第37編1条56項に定義される特許性に肝要な情報について開示義務があることを認めます。

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56.

Japanese Language Declaration

私は米国法典第35編119条(a)-(d)あるいは365条(b)に基づき特許あるいは発明者証書の下記外国出願、または365条(a)に基づき米国以外の少なくとも1ヶ国を指定した下記PCT外国出願についての外国優先権をここに主張するとともに、下記項目にx印を付けることにより優先権を主張する出願以前の出願日を有する特許あるいは発明者証書の外国出願あるいはPCT外国出願を示します。

I hereby claim foreign priority under Title 35, United States Code, § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below, and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

Prior foreign application(s)
外国での先行出願

(Number) (番号)	(Country) (国名)	(Day/Month/Year Filed) (出願年月日)	Priority Claimed 優先権の主張 Yes 有り	No 無し
11/181142	Japan	June 28, 1999	☑	☐
			☐	☐

私は米国法典第35編119条(e)に基づき下記の米国仮特許の利益をここに主張します。

I hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below.

(Application No.) (出願番号)	(Filing Date) (出願日)

私は米国法典第35編120条に基づき下記米国特許出願、あるいは365条(c)に基づき米国を指定する下記PCT国際特許出願の利益をここに主張し、本特許出願内特許請求範囲の各項目の内容が米国法典第35編112条の最初の項に規定される方法により先行米国あるいはPCT国際特許出願で開示されていない限りにおいて連邦規則法典第37編1条56項に定義される特許性に肝要で、先行特許出願の出願日から本特許出願の国内あるいはPCTの出願日までの間に入手された情報について開示義務があることを認めます。

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

(Application No.) (出願番号)	(Filing Date) (出願日)	(Status: patented, pending, abandoned) (状態：特許成立済、係属中、放棄済)

私は本宣言書内で私自身の知識に基づいてなされたすべての陳述が真実であり、情報および信ずるところに基づいてなされたすべての陳述が真実であると信じられていることをここに宣言し、さらに故意になされた虚偽の陳述等々は米国法典第18編1001条に基づき罰金あるいは拘禁または両方による処罰にあたり、またかような故意による虚偽の陳述はそれに基づく特許出願あるいは成立特許の有効性を危うくする可能性があることを認識した上でこれらの陳述をなしたことを宣言します。

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Japanese Language Declaration

委任状：私は下記の米国特許商標局（USPTO）顧客番号のもとに記載されるSUGHRUE MION法律事務所のすべての弁護士を、同顧客番号のもとに記載される個々の弁護士はSughrue Mion法律事務所のみの自由裁量に基づき変更され得ることを認識した上で、本特許出願の手続きおよびそれに関わる特許商標局との業務を遂行する弁護士として指名し、本特許出願に関するすべての通信が同USPTO顧客番号のもとに提出された住所宛に送付されることを要請します。

POWER OF ATTORNEY: I hereby appoint all attorneys of SUGHRUE MION, PLLC who are listed under the USPTO Customer Number shown below as my attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith, recognizing that the specific attorneys listed under that Customer Number may be changed from time to time at the sole discretion of Sughrue Mion, PLLC, and request that all correspondence about the application be addressed to the address filed under the same USPTO Customer Number.

23373

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